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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,032	12/17/1999	ANDREAS BERGMANN	PM263260	3417

909 7590 09/02/2003

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	21

DATE MAILED: 09/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,032	BERGMANN ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13 and 23-32* is/are pending in the application.

4a) Of the above claim(s) *13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 13 and 23-32 are pending.

2. Claim 13 stands withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected invention.

3. In view of the amendment filed 6/18/03, the following rejections remain.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 23-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for determination of TSH receptor autoantibodies comprising" (i) reacting a solid phase, comprising an affinity-purified immobilized recombinant human TSH receptor, with a liquid biological sample to be assayed for the presence of said autoantibodies; (ii) separating a reacted solid phase from the liquid biological samples; (iii) washing the reacted solid phase; (iv) incubating the reacted solid phase with a buffer solution comprising an amount of labeled bovine TSH for a sufficient time to occupy all the TSH binding sites of the recombinant human receptor not occupied by the autoantibodies; and (v) determining the presence and/or amount of the autoantibodies on the basis of the amount of labeled bovine TSH bound to the solid phase; wherein the human recombinant TSH receptor is immobilized to a solid support by a specific antibody that binds specifically to the human TSH receptor and recognizing the conformational epitope such as the ones disclosed on page 31 of the specification; (2) A method for the determination of TSH receptor autoantibodies comprising: (i) reacting a solid phase comprising an affinity-purified immobilized recombinant human TSH receptor with a solution prepared from: (a) a serum-containing biological sample to be assayed for the presence of said autoantibodies, and (b) a buffer solution containing labeled bovine TSH for a sufficient time to occupy all the TSH binding sites of the human TSH receptor not occupied by the autoantibodies; (ii) separating the solution from a reacted solid phase; (iii) washing the reacted solid phase; and (iv) determining the presence and/or amount of the autoantibodies on the basis of

the amount of labeled bovine TSH bound to the solid phase; wherein the recombinant human TSH receptor is immobilized to a solid support by a specific antibody that binds specifically to the human TSH receptor and recognizing the conformational epitope such as the ones disclosed on page 31 of the specification; (3) the said methods wherein the solid phase is formed by the walls of test tubes, which are precoated with said human TSH receptor specific antibody; (4) the said methods wherein the antibody against the specific human TSH receptor is a monoclonal antibody for detecting TSH receptor-stimulating antibodies in human serum associated with Graves' disease, **does not** reasonably provide enablement for any method for the determination of any TSH receptor autoantibodies as set forth in claims 23-32 using any selective antibody against the human TSH receptor, any monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor and is obtained by immunizing an animal with any DNA plasmid construct encoding the human TSH receptor for detecting TSH receptor-stimulating antibodies in human serum associated with Graves' disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method for determining human TSH receptor stimulating autoantibodies comprising the steps of: (i) immobilized recombinant human TSH receptor (rhTSHR) to a solid phase such as a test tube using a conformational dependent antibody that binds specifically to the human TSH receptor such as the ones disclosed on page 31 of the specification; (ii) incubating the immobilized rhTSHR test tube with a liquid biological sample to be assayed for the presence of TSH receptor autoantibodies; (iii) washing the reacted solid phase; (iv) incubating the reacted solid phase with a buffer solution comprising an amount labeled bovine TSH and (iv) determining the presence and amount of the autoantibodies on the basis of the amount of labeled bovine TSH bound to the solid support.

The specification does not teach how to determine TSH receptor stimulating autoantibodies, which are characteristic of Grave's disease, using *any* monoclonal antibody that recognizes only conformational epitopes of the receptor by immunizing an animal with *any* "TSH receptor-DNA construct". There is insufficient guidance as to the structure such as the specific nucleotide in the DNA plasmid that encode which part of the TSH receptor, in turn, the antibody generated from immunizing with said plasmid would produce antibody that binds specifically only to the "conformational epitopes" of the human TSH receptor. Note that the selective antibody "recognizes" more than one conformational epitopes on the human TSH receptor. Further, the specification on page 15 defines rhTSHR represent any recombinant complete, more or less glycosylated polypeptide, a partial sequence of a sufficient length or a genetically engineered fusion product. Given that the DNA plasmid encoding the human TSH receptor wherein the receptor could be a partial sequence of a sufficient length or a genetically engineered fusion product, there is insufficient guidance as to the structure or the immunogen, the binding specificity of the selective antibody. Without the specific DNA plasmid construct, it would take undue amount of experimentation even for one skill in the art to make and use such antibody for the claimed method of detecting TSH receptor autoantibodies. Further, there is insufficient working example demonstrating that any "DNA plasmid construct" would generate antibody that recognizes only conformational epitopes of the human TSH receptor, in turn, would be useful for a method of detecting TSH receptor autoantibodies.

Harlow *et al*, of record, teach that the ability of an antibody to bind to a particular epitope on a protein is highly dependent on the overall structure of the protein itself and the corresponding DNA encoding that protein.

Stryer *et al*, of record, teach that the primary amino acid sequence determines the conformational of the protein (See enclosed relevant pages).

Kuby *et al*, of record, teach that immunizing a peptide such as a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Colman *et al,* of record, teach that even a single amino acid changes within the interface of an antibody-antigen can raise or lower the affinity of the antibody (See page 33, in particular). Given the indefinite number of undisclosed animal protein, it is unpredictable which undisclosed protein or immunogen will generate "animal-specific" antibody that would bind specifically to

the human TSH receptor, in turn, useful for immobilize the human TSH receptor to the solid phase as a method the determination of TSH receptor stimulating autoantibodies. Likewise, given the indefinite number of undisclosed conformational dependent epitope encoded by the undisclosed TSH receptor-DNA construct, it is unpredictable which undisclosed conformational epitope encoded by *any* "TSH-receptor-DNA construct" would be useful for generating human TSH receptor specific antibody that recognizes the "conformational dependent epitope", in turn, would be useful for determining the human TSH receptor-stimulating autoantibodies whose occurrence in human is characteristic of Grave's disease.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 6/18/03 have been fully considered but are not found persuasive.

Applicants' position is that the concern over "an animal specific antibody" has been addressed by amended claims.

However, claims 23 and 24 still recite selective antibody against the human TSH receptor. Further, claim 26 recites that the selective antibody against the human TSH receptor is a monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor and is obtained by immunizing an animal with a DNA plasmid construct encoding the human TSH receptor. There is insufficient guidance as to the structure such as the specific nucleotide in the DNA plasmid that encode which part of the TSH receptor, in turn, the antibody generated from immunizing with said plasmid would produce antibody that binds specifically only to the "conformational epitopes" of the human TSH receptor. Note that the selective antibody "recognizes" more than one conformational epitopes on the human TSH receptor. Further, the specification on page 15 defines rhTSHR represent any recombinant complete, more or less glycosylated polypeptide, a partial sequence of a sufficient length or a genetically engineered fusion product. Given that the DNA plasmid encoding the human TSH receptor wherein the

receptor could be a partial sequence of a sufficient length or a genetically engineered fusion product, there is insufficient guidance as to the structure of the immunogen, much less about the binding specificity of the selective antibody. Without the specific DNA plasmid construct, it would take undue amount of experimentation even for one skill in the art to make and use such antibody for the claimed method of detecting TSH receptor autoantibodies. Further, there is insufficient working example demonstrating that any "DNA plasmid construct" would generate antibody that recognizes only conformational epitopes of the human TSH receptor, in turn, would be useful for a method of detecting TSH receptor autoantibodies. As applicant put it on page 6 of the response, how could the skilled artisan be expected to obtain antibodies that recognize the conformation epitopes when immunized with any DNA plasmid encoding receptor fragments that were not functional TSH receptors and did not compete with TSH and/or were not active in cell stimulation process for a method of detecting autoantibodies wherein the autoantibodies are receptor-stimulating autoantibodies whose occurrence in a human serum is characteristic of Graves' disease?

6. Claims 23-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any method for the determination of any TSH receptor autoantibodies as set forth in claims 23-32 using any selective antibody against the human TSH receptor, any monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor and is obtained by immunizing an animal with any DNA plasmid construct encoding the human TSH receptor for detecting TSH receptor-stimulating antibodies in human serum associated with Graves' disease.

The specification discloses only a method for determining human TSH receptor stimulating autoantibodies comprising the steps of: (i) immobilized recombinant human TSH receptor (rhTSHR) to a solid phase such as a test tube using a conformational dependent antibody that binds specifically to the human TSH receptor such as the ones disclosed on page 31 of the specification; (ii) incubating the immobilized rhTSHR test tube with a liquid biological sample to be assayed for the presence of TSH receptor autoantibodies; (iii) washing the reacted solid phase; (iv) incubating the reacted solid phase with a buffer solution comprising an amount labeled

bovine TSH and (iv) determining the presence and amount of the autoantibodies on the basis of the amount of labeled bovine TSH bound to the solid support. Further, the specification on page 15 defines rhTSHR represent any recombinant complete, more or less glycosylated polypeptide, a partial sequence of a sufficient length or a genetically engineered fusion product.

Other than the specific DNA construct used to generate monoclonal antibody that binds specifically to human TSH receptor recognizing the conformational epitope, there is inadequate written description about the structure associated with function of any "TSH receptor-DNA construct" that used to generate antibody that recognizes the conformational epitope of human TSH receptor as a method for the determination of TSH receptor autoantibodies wherein the autoantibodies are receptor-stimulating autoantibodies whose occurrence in a human serum is characteristic of Graves' disease. Given the lack of any additional representative DNA plasmid construct for the claimed method, one skill in the art would recognize that Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 6/18/03 have been fully considered but are not found persuasive.

Applicants' position is that the concern over "an animal specific antibody" has been addressed by amended claims.

However, claims 23 and 24 still recite selective antibody against the human TSH receptor. Further, claim 26 recites that the selective antibody against the human TSH receptor is a monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor and is obtained by immunizing an animal with a DNA plasmid construct encoding the human TSH receptor. There is insufficient guidance as to the structure such as the specific nucleotide in the DNA plasmid that encode which part of the TSH receptor, in turn, the antibody generated from immunizing with said plasmid would produce antibody that binds specifically only to the "conformational epitopes" of the human TSH receptor. Note that the selective antibody "recognizes" more than one conformational epitopes on the human TSH receptor. Further, the specification on page 15 defines rhTSHR represent any recombinant complete, more or less glycosylated polypeptide, a partial sequence of a sufficient length or a genetically engineered

fusion product. Given that the DNA plasmid encoding the human TSH receptor wherein the receptor could be a partial sequence of a sufficient length or a genetically engineered fusion product, there is insufficient guidance as to the structure of the immunogen, the binding specificity of the selective antibody. Without the specific DNA plasmid construct, it would take undue amount of experimentation even for one skill in the art to make and use such antibody for the claimed method of detecting TSH receptor autoantibodies. Further, there is insufficient working example demonstrating that any "DNA plasmid construct" would generate antibody that recognizes only conformational epitopes of the human TSH receptor, in turn, would be useful for a method of detecting TSH receptor autoantibodies.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 23-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vitti *et al* (Acta Med Austriaca 23(1-2): 52-6, 1996; PTO 892) or US Pat No. 5,614,363 (March 1997, PTO 892) each in view of Harlow et al (in Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory 1988, pages 556, 564-591), Nicholson e*t al* (J Mol Endocrinol 16(2): 159-70, 1996; PTO 892) and/or Morgenthaler *et al* (of record, J Clin Endocrinol Metab 81(2):700-6, Feb 1996, PTO 892).

Vitti *et al* teach a method for the determination of TSH receptor autoantibodies where the autoantibodies mimic TSH (thyroid stimulating antibody) found in Grave's disease (See page 53,

column 1, in particular) using human thyrotropin receptor expressing cell line such as CHO cells that has been transfected with cDNA encoding the human thyrotropin receptor (See abstract, in particular). The reference method comprises the steps of immobilized the TSH receptor expressing cell to a solid phase such as petri dishes (See page 53, column 2, Cell culture, in particular), TSH-receptor antibodies (TRAb) are measured by a commercial radioreceptor assay based on inhibition of binding of 125iodine bovine TSH to porcine TSH-receptor or solubilized human TSH receptor on CHO cells using commercially available assay (TRAK assay, page 53, TSH-receptor Antibodies (TRAb), in particular). Vitti *et al* teach most autoantibodies to TSH receptor are measured by their ability to inhibit the binding of radiolabeled TSH to its receptor present in solubilized thyroid membrane preparations (See page 53, column 1, in particular).

The '363 patent teaches recombinant human TSH receptor for detection of auto-antibodies found in Graves' patients in the form of a competitive binding assay employing radiolabeled TSH and TSH receptor (See column 7, lines 8-63, column 8, lines 3-11, claim 9 of '363, in particular). The reference purified recombinant human TSH receptor is immunobilized on a support matrix (See column 9, line 24-38, in particular).

The claimed invention as recited in claims 23-24 differs from the references only that the method for the determination of TSH receptor autoantibodies comprising immobilized affinity purified recombinant human TSH receptor to a solid support by an antibody against the receptor.

The claimed invention as recited in claim 25 differs from the references only that the method wherein the solid phase is formed by the walls of the test tubes, which are precoated with an animal-specific antibody for binding the selective antibody against the receptor.

The claimed invention as recited in claim 26 differs from the references only that the method for the determination of TSH receptor autoantibodies wherein the selective antibody against the receptor is a monoclonal antibody that recognizes only conformational epitopes of the receptor and is obtained by immunizing an animal with a TSH receptor-DNA construct.

Harlow *et al* teach various immunoassays for detecting and quantitating any antibodies in a sample or test solution wherein the reference antigen (the TSH receptor in this case) is immobilized to a solid support such as test tube, or multi-well plate using an antibody that binds specifically to the antigen. The test solution or dilution of the test solution (with buffer) containing an unknown amount of antibody such as the auto-TSH receptor antibody is added. Antibodies in the test solution are allowed to bind to the immobilized antigen in the present of radiolabeled TSH and unbound antibodies are removed by washing. The presence of the bound

antibodies is detected by direct counting using a gamma counter based on competitive binding of radiolabeled TSH to the TSH receptor. Harlow *et al* teach the advantages of antibody sandwich immunoassays are: it is rapid and easy, quantitative, and sensitive with detection limit about 0.01 to 0.1 ng (See page 584, in particular).

Nicholson *et al* teach various human TSH receptor antibodies such as A7, A8, A9, A10 and A11 that bind to various epitopes localized to various regions on the human TSH receptor (See entire document, page 168, in particular). The reference monoclonal antibodies such as A10 and A11 recognizes the conformational epitopes of the receptor since it binds only to acetone fixation and not by PLP fixation of thyroid section, suggesting the reference antibody recognizes the conformational epitope of the human TSH receptor (See abstract, in particular). The reference human TSH receptor is produced by various cDNA constructs in insect cells as well as in Escherichia coli (See page 160, in particular). The reference antibodies are produced by immunizing mice with the human TSH receptors produced by the cDNA constructs (See production of mAbs, in particular). Nicholson *et al* teach the reference antibodies are useful for radiolabeled TSH to porcine membranes in a radioreceptor assay (See Abstract, in particular).

Morgenthaler *et al* teach antibodies such as A7, A9 and A10 that bind specifically to the recombinant human TSH receptor for detecting TSH receptor autoantibodies in Graves' disease (See entire document; abstract, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to immobilized the recombinant human TSH receptor as taught by the '363 patent using the monoclonal antibody that binds specifically to the human TSH receptor as taught by Nicholson *et al* and Morgenthaler *et al* or to substitute the human TSH receptor expressing cell lines as taught by the Vitti *et al* for the recombinant human TSH receptor as taught by the '363 patent and immobilized said TSH receptor using the monoclonal antibody that binds specifically to the human TSH receptor as taught by Nicholson *et al* or Morgenthaler *et al* for a method for determining TSH receptor autoantibodies as taught by Harlow *et al*, and Vitti *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach that the advantages of antibody sandwich immunoassays are: it is rapid, easy, quantitative, and sensitive with a detection limit about 0.01 to 0.1 ng (See page 584, in particular). Nicholson *et al* teach the reference antibodies are useful for radiolabeled TSH to

porcine membranes in a radioreceptor assay (See Abstract, in particular). Morgenthaler *et al* teach antibodies such as A7, A9 and A10 to recombinant human TSH receptor are useful for detecting TSH receptor autoantibodies in Graves' disease (See entire document; abstract, in particular). Claim 26 is included in this rejection because Nicholson e*t al* teach the cDNA construct encoding the human TSH receptor and immunizing either the protein encoded by the reference cDNA construct or the reference cDNA construct would produce the same monoclonal antibody that recognizes the conformational epitope of the receptor.

Applicants' arguments filed 6/18/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) any combination of Vitti et al or the '363 patent in view of Harlow et al, Nichoson and/or Morgenthaler et al is based on impermissible hindsight and does not render the present invention obvious. (2) The secondary references fail to demonstrate why the skilled artisan would have been motivated to combine them with the primary references or even that such a combination would work. (3) To obtained TSH receptors and receptor fragments were not functional TSH receptors (i.e. they did not compete with TSH and/or were not active in cell stimulation tests). Further, Nicholson et al discusses attempts to express recombinant TSH receptors in insect cells and E coli. The obtained receptors or receptor fragments were not functional TSH receptors (i.e. they did not compete with TSH and/or were not active in cell stimulation tests). Neither the obtained receptors or receptor fragments or the antibodies obtained using said receptors or receptor fragments were ever successfully used in a solid phase assay for human TSH receptor autoantibodies in a biological fluid. The '461 patent does not render the present invention obvious. The '461 patent acknowledges the difficulties of designing a solid phase assay for the determination of TSH receptor antibodies and set out to avoid such a procedure.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no motivation to combine or that such a combination would work, specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA). Further, obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). See MPEP 2143.02.

In response to applicant's argument that neither the TSH receptors, nor receptor fragments functional TSH receptors (i.e. they did not compete with TSH and/or were not active in cell stimulation tests) or the antibodies obtained using said receptors or receptor fragments were ever successfully used in a solid phase assay for human TSH receptor autoantibodies in a biological fluid, it is noted that the features upon which applicant relies (i.e., functional TSH receptor, functional receptor fragment) are not recited in the rejected claims 23-29 and 31-32. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, it is noted that the selective antibody against the human TSH receptor in claims 23-32 is *any* antibody that binds to human TSH receptor and not functional human TSH receptor.

10. Claims 23-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,814,461 (of record, Sept 1998, PTO 892) in view of US Pat No. 5,614,363 (March 1997, PTO 892), Harlow et al (in Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory 1988, pages 556, 564-591), Nicholson e*t al* (J Mol Endocrinol 16(2): 159-70, 1996; PTO 892) or Morgenthaler *et al* (of record, J Clin Endocrinol Metab 81(2):700-6, Feb 1996, PTO 892).

The '461 patent teaches a method for detecting autoantibodies to the human thyroid stimulating hormone (TSH) receptor in a biological fluid sample (serum) from patient with Graves' disease using a solid phase competitive receptor binding assay (See entire document). The reference method comprises the steps of immobilize the TSH such as bovine TSH rather than recombinant human TSH receptor to the solid support such as test tube using anti-TSH antibody (See column 7, material and methods in particular). The TSH receptor autoantibodies from

patient serum sample is allowed to react with the TSH on the solid support (See column 9, line 27) in the presence of labeled porcine TSH receptor as binder (see column 9, line 25 in particular), luminescence labeled bovine or human anti-TSH specific monoclonal antibody as tracer wherein said antibody selectively binds to the free TSH but not the bound TSH (Column 7, line 12; column 9, line 30 in particular), and bovine TSH as competitor (See column 7 line 11 in particular). The TSH specific antibodies include bovine specific monoclonal antibody (See column 7, line 40 in particular) and human TSH specific antibody (See column 7, line 20 in particular). Prior to assay, the luminescence labeled anti-TSH specific monoclonal antibody (tracer) is immobilized to the solid phase such as the test tube wherein the receptor binding assay is carried out as a one-step method where TSH antibody is directly labeled (See material and method in particular) or as a two-step method where TSH is bound to the solid phase and the TSH receptor binding is detected with a labeled second monoclonal anti-TSH antibody (See Fig 1; claims 1 and 5 in particular). The patient sample containing TSH autoantibodies is preincubated with the porcine TSH receptor in the presence of bovine TSH competitor (for specific binding); the liquid fraction is then transfer to the test tube that has been coated with anti-TSH specific antibody. After incubation and washing, the displacement of the specific binding of tracer amounts of labeled bovine or human TSH is measured in a manner well known in the art and the amount bTSH detected is proportional to the amount of autoantibodies in the patient sample (See column 9, line 25 and claims in particular). Furthermore, the '461 teaches that TSH receptor assays function very much similar to competitive radioimmunoassays where TSH receptors are used as specific binding reagent for autoantibodies and radiolabeled TSH as tracer (See column 3, line 32 bridging column 4 in particular).

The claimed invention as recited in claims 23-24 differs from the reference only that the method for the determination of TSH receptor autoantibodies comprising immobilized affinity purified recombinant human TSH receptor rather than the TSH to a solid support by an antibody against the receptor.

The claimed invention as recited in claim 25 differs from the reference only that the method wherein the solid phase is formed by the walls of the test tubes, which are precoated with an animal-specific antibody for binding the selective antibody against the receptor.

The claimed invention as recited in claim 26 differs from the reference only that the method for the determination of TSH receptor autoantibodies wherein the selective antibody

against the receptor is a monoclonal antibody that recognizes only conformational epitopes of the receptor and is obtained by immunizing an animal with a TSH receptor-DNA construct.

The '363 patent teaches recombinant human TSH receptor for detection of auto-antibodies found in Graves' patients in the form of a competitive binding assay employing radiolabeled TSH and TSH receptor (See column 7, lines 8-63, column 8, lines 3-11, claim 9 of '363, in particular). The reference purified recombinant human TSH receptor is immunobilized on a support matrix (See column 9, line 24-38, in particular).

Harlow *et al* teach various immunoassays for detecting and quantitating any antibodies in a sample or test solution wherein the reference antigen (the TSH receptor in this case) is immobilized to a solid support such as test tube, or multi-well plate using an antibody that binds specifically to the antigen. The test solution or dilution of the test solution (with buffer) containing an unknown amount of antibody such as the auto-TSH receptor antibody is added. Antibodies in the test solution are allowed to bind to the immobilized antigen in the present of radiolabeled TSH and unbound antibodies are removed by washing. The presence of the bound antibodies is detected by direct counting using a gamma counter based on competitive binding of radiolabeled TSH to the TSH receptor. Harlow *et al* teach the advantages of antibody sandwich immunoassays are: it is rapid and easy, quantitative, and sensitive with detection limit about 0.01 to 0.1 ng (See page 584, in particular).

Nicholson *et al* teach various human TSH receptor antibodies such as A7 through A11 that bind to various epitopes localized to various regions on the human TSH receptor (See entire document, page 168, in particular). The reference monoclonal antibodies such as A10 and A11 recognizes the conformational epitopes of the receptor since it binds only to acetone fixation and not by PLP fixation of thyroid section, suggesting the reference antibody recognizes the conformational epitope of the human TSH receptor (See abstract, in particular). The reference human TSH receptor is produced by various cDNA constructs in insect cells as well as in Escherichia coli (See page 160, in particular). The reference antibodies are produced by immunizing mice with the human TSH receptor produced by the cDNA constructs (See production of mAbs, in particular). Nicholson e*t al* teach the reference antibodies are useful for radiolabeled TSH to porcine membranes in a radioreceptor assay (See Abstract, in particular).

Morgenthaler *et al* teach various monoclonal antibodies such as A7, A9 and A10 and polyclonal antibodies to recombinant human TSH receptor for detecting TSH receptor autoantibodies in Graves' disease (See entire document; abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the TSH as taught by the '461 patent for the recombinant TSH receptor as taught by the '363 patent for a method for determining TSH receptor autoantibodies as taught by the '461 patent and Harlow *et al* by immobilized the recombinant human TSH receptor as taught by the '363 patent using the monoclonal antibody that binds specifically to the human TSH receptor as taught by Nicholson *et al* or Morgenthaler *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach advantages of antibody sandwich immunoassays are: it is rapid and easy, quantitative, as well as sensitive with a detection limit about 0.01 to 0.1 ng (See page 584, in particular). Nicholson e*t al* teach the reference antibodies are useful for radiolabeled TSH to porcine membranes in a radioreceptor assay (See Abstract, in particular). Morgenthaler *et al* teach antibodies such as A7, A9 and A10 to recombinant human TSH receptor are useful for detecting TSH receptor autoantibodies in Graves' disease (See entire document; abstract, in particular). The '363 patent teaches human anti-TSH receptor autoantibodies in Graves' would bind to the human recombinant TSH receptor with improved specificity and sensitivity over the currently available assays which generally use the porcine TSH receptor (See column 7, line 31, in particular). Claim 26 is included in this rejection because Nicholson e*t al* teach the cDNA construct encoding the human TSH receptor and immunizing either the protein encoded by the reference cDNA construct or the reference cDNA construct would produce the same monoclonal antibody that recognizes the conformational epitope of the receptor.

Applicants' arguments filed 6/18/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) any combination of Vitti et al or the '363 patent in view of Harlow et al, Nichoson and/or Morgenthaler et al is based on impermissible hindsight and does not render the present invention obvious. (2) The secondary references fail to demonstrate why the skilled artisan would have been motivated to combine them with the primary references or even that such a combination would work. (3) To obtained TSH receptors and receptor fragments were not functional TSH receptors (i.e. they did not compete with TSH and/or were not active in cell stimulation tests). Further, Nicholson et al discusses attempts to express recombinant TSH receptors in insect cells and E coli. The obtained receptors or receptor fragments were not

functional TSH receptors (i.e. they did not compete with TSH and/or were not active in cell stimulation tests). Neither the obtained receptors or receptor fragments or the antibodies obtained using said receptors or receptor fragments were ever successfully used in a solid phase assay for human TSH receptor autoantibodies in a biological fluid. The '461 patent does not render the present invention obvious. The '461 patent acknowledges the difficulties of designing a solid phase assay for the determination of TSH receptor antibodies and set out to avoid such a procedure.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no motivation to combine or that such a combination would work, specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA). Further, obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). See MPEP 2143.02.

In response to applicant's argument that neither the TSH receptors, nor receptor fragments functional TSH receptors (i.e. they did not compete with TSH and/or were not active in cell stimulation tests) or the antibodies obtained using said receptors or receptor fragments were ever successfully used in a solid phase assay for human TSH receptor autoantibodies in a biological fluid, it is noted that the features upon which applicant relies (i.e., functional TSH receptor, functional receptor fragment) are not recited in the rejected claims 23-29 and 31-32. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir.

1993). Further, it is noted that the selective antibody against the human TSH receptor in claims 23-32 is *any* antibody that binds to human TSH receptor and not functional human TSH receptor.

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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